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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant:	Frederick M. Ausubel et al.	Art Unit:	1645
Serial No.:	08/962,750	Examiner:	R. Swartz
Filed:	November 3, 1997	Customer No.:	21559
Title:	METHODS OF SCREENING COMPOUNDS USEFUL FOR PREVENTION OF INFECTION OR PATHOGENICITY		

Box Appeal  
Commissioner of Patents and Trademarks  
Washington, DC 20231

APPELLANTS' REPLY BRIEF  
SUBMITTED PURSUANT TO 37 CFR § 1.193

In response to the Examiner's Answer mailed on September 9, 2002,  
appellants submit, in triplicate, the following Reply Brief.

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*In re Sang-Su Lee*, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002)

*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985)

### **Status of Claims**

Following the Examiner's Answer, claims 1-24, 26, and 28-30 are currently pending. Claims 25 and 27 have been canceled. Claims 31-45 have been withdrawn from consideration as not directed to the elected invention. Claims 1-24, 26, and 28-30 were finally rejected in the Final Office Action mailed on October 14, 1999 and are appealed.

### **Status of Amendments**

Appellants' amendment filed with their Reply of July 21, 1999 has been entered. The amendment filed concurrently with the Notice of Appeal on April 14, 2000 was not entered.

A Supplemental Amendment that limits the issues on appeal was filed with appellants' Brief on Appeal mailed on February 15, 2001. This Supplemental Amendment was not considered in the Examiner's Answer mailed on September 9, 2002. For the reasons explained below, appellants request entry of this amendment and consideration of the appeal based on the claims in Appendix B of appellants' Brief on Appeal mailed on February 15, 2001. Alternatively, if the amendment is not entered, appellants' appeal is based on the claims as they presently stand in this case, which are found in Appendix A of appellants' Brief on Appeal mailed on February 15, 2001.

### **Grouping of Claims**

For the purpose of this appeal, the claims are grouped as follows: Group I (claims 1-5); Group II (claim 6 and claims dependent thereon); Group III (claim 7 and claims dependent thereon); Group IV (claim 12); Group V (claim 13); Group VI (claim 14); Group VII (claim 15 and claims dependent thereon); Group VIII (claims 20 and 21); Group IX (claims 22-24, 26, and 28); and Group X (claims 29-30). In view of the differences discussed in more detail below, these groups present different issues on the question of obviousness and should be considered separately. Accordingly, the claims on appeal do not stand or fall together, and should be evaluated based on the aforementioned groups.

### **Argument**

The pending claims stand rejected under 35 U.S.C. § 103. The appellants' response to this rejection and the issues raised by the Office in the Examiner's Answer are presented below.

### **Entry of Amendment**

Appellants respectfully request entry of the Supplemental Amendment mailed on February 15, 2001 with the appellants' Brief on Appeal. This amendment, which, with respect to claims 1 and 22, is identical to that submitted by appellants with their reply of April 14, 2000, narrows the issues on appeal and expedites resolution of this case. This amendment raises no issues requiring a new search, as the Office's initial

search is believed to have covered the common virulence factor concept embodied in appellants' claims as originally filed and as disclosed in appellants' specification. (See, for example, appellants' specification, at page 3, under the heading "Summary of Invention," where it is stated: "We have discovered that common pathogenic virulence factors are involved in infection and pathogenicity of both animal and plant hosts.") Similarly, the amendment does not raise any issue relating to the addition of new matter.

With respect to the statement made in the Examiner's Answer that the claims do not distinguish between compounds which inhibit or reduce pathogenicity by affecting the function of a common virulence factor (versus affecting the function of multiple virulence factors), appellants respectfully point out that the amended claims do make this distinction. In particular, paragraph (b) of amended claims 1 and 22 requires identifying a compound that inhibits or reduces pathogenicity of the same pathogen in the two different hosts as a consequence of affecting the function of said common virulence factor in said same pathogen. Accordingly, it is appellants' position that this amendment does no more than narrow the issues on appeal, and on this basis request its entry.

**Rejection under 35 U.S.C. § 103(a)**

Claims 1-24, 26, and 28-30 stand rejected under § 103(a) in view of several references presently made of record in this case. For the following reasons, this rejection, as applied to the claims found in either Appendix A or B of appellants' Brief on Appeal mailed on February 15, 2001, should be withdrawn.

In the Office's Answer, the Examiner again concludes that it was obvious at the time the invention was made to test drug efficacy of a variety of suspected compounds for controlling or eradicating the presence of *Pseudomonas* in both plants and animals. This conclusion is based entirely on anecdotal evidence found in the references of record: In short, the Examiner asserts that, since *Pseudomonas* lives on plant and animal hosts, it is obvious to screen for drugs using both hosts. But nowhere does the Examiner identify any scientific principle or theory found in the references to suggest the claimed invention. Indeed, none of the references of record so much as mentions using two different eukaryotic organisms together for screening therapeutics that inhibit or reduce pathogenicity of the same pathogen on different hosts, nor do the references provide any scientific rationale that would motivate the skilled worker to conduct such screens.

While five references are relied upon for this rejection, the Office presents no specific motivation for their combination. To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires an Examiner to show a motivation to combine the references that create the case of obviousness. See, e.g., *C.R. Bard, Inc. v. M3 Sys., Inc.*, 157 F.3d 1340, 1352, 48 U.S.P.Q.2d 1225, 1232 (Fed. Cir. 1998) (describing "teaching or suggestion or motivation [to combine]" as an "essential evidentiary component of an obviousness holding"); *In re Rouffet*, 149 F.3d 1350, 1359, 47 U.S.P.Q.2d 1453, 1459 (Fed. Cir. 1998) ("the Board must identify specifically . . . the reasons one of ordinary skill in the art would have been motivated to select the references and combine them"); *In re Fritch*, 972 F.2d 1260, 1265, 23 U.S.P.Q.2d 1780, 1783 (Fed.

Cir. 1992) (examiner can satisfy burden of obviousness in light of combination “only by showing some objective teaching [leading to the combination]”); *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596, 1600 (Fed. Cir. 1988) (evidence of teaching or suggestion “essential” to avoid hindsight); *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 297, 227 U.S.P.Q. 657, 667 (Fed. Cir. 1985) (district court’s conclusion of obviousness was error when it “did not elucidate any factual teachings, suggestions or incentives from this prior art that showed the propriety of combination”). Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor’s disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. See, e.g., *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138, 227 U.S.P.Q. 543, 547 (Fed. Cir. 1985) (“The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.”)

This standard has not been met in the present case. As explained in detail below, no specific motivation has been provided for the prior art combination except the statement at page 9 of the Answer that:

In this case, the cited references teach that *Pseudomonas* is a pathogen frequently involved in disease in both plants and animals, and that transmission of *Pseudomonas* to patients in hospitals may be through ingestion of infected agricultural plants. Because of this nexus, it would have been obvious at the time of the invention was made to a person having ordinary skill in the art to test drug efficacy of a variety of suspected compounds for controlling or eradicating the presence of *Pseudomonas* in both plants and animals. In addition, it would have been obvious to utilize models of both plants and animals in order to identify such compounds.



This statement does not rise to the requisite standard for specific motivation to combine references. As stated by the Federal Circuit, the evidence of a suggestion, teaching, or motivation to combine “must be clear and particular.” *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999). “‘Common knowledge and common sense’ even if assumed to derive from the agency’s expertise, do not substitute for authority when the law requires authority...The board [or Patent Office] cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it relies.” *In re Sang-Su Lee*, 277 F.3d 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). The motivation to combine references “must be based on objective evidence of record.” *Lee*, 277 F.3d at 1343, 61 U.S.P.Q.2d at 1433. “This precedent has been reinforced in myriad decisions, and cannot be dispensed with.” *Id.* Because no specific motivation has been set forth by the Office for the rejection of the claims on appeal, this rejection must be withdrawn. Appellants now turn to the references discussed in the Examiner’s Answer.

### Elrod

Elrod, the primary reference, clearly teaches away from the combination of references. Although Elrod recognized that the pathogen, *Pseudomonas aeruginosa*, is capable of infecting both humans and plants, Elrod, unlike appellants, concluded that such dual pathogenicity resulted, not from the existence of common virulence factors

found in the bacterium, but rather from the existence of different virulence factors, and possibly even from the existence of different strains of the same bacterium, each being responsible for causing infection in either a plant or a human. Evidence for this assertion is found, for example, at page 642 of the Elrod teaching, where the reference clearly states (emphasis added):

It appears likely that the **phytotoxic [plant pathogenic] factors** of the organism [*P. aeruginosa*] **are not the same as the toxin substances that induce animal disease**. This was emphasized by the action of **rough variants** which, though not fatal to animals, retained their pathogenicity for plants.

Accordingly, there is clear evidence in the Elrod article of teaching away from the method claimed by appellants. Unlike appellants, who discovered that there are common virulence factors needed to cause disease in plants and animals, Elrod teaches that “the phytotoxic factors of the organism are not the same as the toxic substances that induce animal disease.” It follows then that Elrod teaches that different mechanisms are responsible for effecting disease in animal and plant hosts. There can be no suggestion to combine when a reference teaches away from its combination with another source. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988). “A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference . . .” *In re Gurley*, 27 F.3d 551, 553, 31 U.S.P.Q.2d 1130, 1131 (Fed. Cir. 1994).

Appellants again note that Elrod fails to provide any reasonable predicate leading to appellants’ claimed invention that utilizes two different hosts to identify

compounds that inhibit or reduce pathogenicity of the same pathogen, and the Examiner has not provided any specific reasoning, in light of this teaching, as to why the invention was obvious to the skilled worker.

If the toxic substances that cause disease in plants and animals are different, as explained by Elrod, then why would one skilled in the art use the two systems to screen for compounds that control or eradicate the presence of *Pseudomonas* in both plants and animals?

In reality, given the Elrod teaching and its failure to demonstrate that toxic substances that cause disease on plants and animals are the same, skilled practitioners would not be motivated to employ plants and animal hosts together when screening for compounds to inhibit a pathogen, as the disease-causing mechanisms are taught to be different.

#### Schroth

Appellants, in response to the Answer, again point out that Schroth, like Elrod, provides no scientific basis for performing appellants' claimed methods. In addition, Schroth fails to recognize that dual pathogenicity of *Pseudomonas* results from the existence of common virulence factors, and absent this recognition this reference is incapable of providing a logical basis for suggesting that effective inhibitory compounds for treating or preventing a pathogen infection in one eukaryotic organism might be identified by screening for those compounds in an entirely different eukaryotic organism.

### Kominos

Kominos fails to teach a single screening method. Appellants again point out that this reference never teaches or suggests that a single pathogen possesses common virulence factors that render it pathogenic on multiple host organisms. Moreover, the finding that certain vegetables serve as a reservoir for *P. aeruginosa* provides no reasonable basis for concluding that screening methods might be developed to identify compounds that inhibit or reduce the pathogenicity of such a pathogen using methods involving two different organisms such as plants and animals, as presently claimed. Kominos does not even teach that *Pseudomonas* is a pathogen of plants.

Kominos, even when combined with Elrod and Schroth, does not teach or suggest appellants' discovery that common pathogenic virulence factors are involved in the infection of widely divergent animal species as well as plants, much less that organisms such as nematodes and plants may be used together to identify compounds that inhibit or reduce the pathogenicity. Again, appellants point out that Kominos, like the other primary references, provides no insight into the disease-causing mechanism and absent such teaching provides no basis for appellants' screening methods.

### Conrad

Appellants again note that, in response to the points raised in the Answer, Conrad does not suggest any aspect of the claimed invention, nor does it provide any motivation for its combination with the primary references. Conrad is singularly focused on determining the efficacy of one particular compound to treat *P. aeruginosa* skeletal

infections in humans. Conrad never even mentions that screening systems apart from the described skeletal system might be used to evaluate the efficacy of the compound, aztreonam, against *Pseudomonas* pathogenicity. Moreover, appellants note that Conrad, like all of the cited references, fails to recognize the existence of common pathogenic virulence factors that facilitate the claimed screening methods in multiple eukaryotic organisms designed to identify therapeutic agents useful for pathogen inhibition or reduction of pathogenicity.

#### Geels

Finally, with respect to Geels, the Office, relying on an apparently out-of-date definition found in Webster's that mushrooms are fungi and fungi are plants, has stated that this reference teaches a "plant model testing a suspected compound for treatment of *Pseudomonas*." Appellants note that Geels teaches "*Pseudomonas tolaasii* control by kasugamycin in cultivated mushrooms (*Agaricus bisporus*)." It is appellants' understanding that mushrooms are classified in the kingdom Fungi, and plants are classified in the kingdom Planta. These organisms are therefore classified in distinct kingdoms and mushrooms are not plants. Accordingly, Geels does not teach a plant model to identify compounds that are efficacious for treating a plant pathogen.

Moreover, appellants note that Geels also does not teach any method of using two different eukaryotic organisms to identify compounds that inhibit or reduce the pathogenicity of the same pathogen. Geels, like all of the other references of record, provides no logical basis, much less the motivation, for developing appellants' claimed

methods.

In sum, despite the significant number of references cited, a *prima facie* case of obviousness has not been established in this case. None of the Elrod, Schroth, Kominos, Conrad, and Geels references is suggestive, alone or in combination, of the use or success of a drug screening system even remotely similar to the one disclosed and claimed by appellants. Indeed, if appellants' claimed invention was obvious in view of these references, someone should have at least suggested it in the fifty-three years between the publication of Elrod in 1942 and the filing of appellants' application in 1995, during which period researchers were searching diligently for new methods of identifying drugs that combat microbial pathogenesis.

Differences between the prior art and the claimed invention are also apparent. See *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459, 467 (1966)("[D]ifferences between the prior art and the claims at issue are to be ascertained.... Against this background, the obviousness or non-obviousness of the claimed invention is determined"). In particular, Elrod discusses different disease-causing mechanisms between plants and animals infected by *Pseudomonas*, while appellants teach that common virulence factors are capable of triggering disease in both. As none of the references provide any reasonable scientific basis for using two organisms together when screening for compounds that inhibit a pathogen, there can be no basis for combining these prior art references to produce the claimed invention.

Only through hindsight — using the claimed invention as a roadmap — is the

Examiner able to arrive at the claimed invention. See *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985) (“It is impermissible to first ascertain factually what [appellants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art”). To believe that one skilled in the art would be motivated to employ appellants’ disclosed methods, especially when the only reference of record that discusses pathogen disease-causing mechanisms, Elrod, teaches away from appellants’ claimed invention, is to assume a level of inspiration constituting inventive activity. The contention that appellants’ claimed screening methods are obvious is unsupported by the cited references, and the Office has not provided reasons as to why a skilled artisan, confronted with the same problem as the inventors, would select the elements from the cited references in the manner claimed.

Appellants submit that the cited references, either alone or in combination, do not render obvious the claims as found in either Appendix A or B. These references fail to teach, suggest, or motivate the use of compound screening methods employing at least two different eukaryotic organisms to identify compounds that inhibit or reduce pathogenicity of the same pathogen. The inventive screening methods resulted from appellants’ crucial scientific discovery that common virulence factors existed, and not from the prior art. Accordingly, appellants respectfully request that the § 103 rejection in this case be withdrawn.

### **Additional Inventive Aspects of the Claims**

Appellants further note that, with respect to the dependent claims, the references of record are even farther afield.

For example, none of the cited references specifically mention or suggest the use of the combination of a vertebrate and a plant (claim 5); a vertebrate and an invertebrate (claim 6); a plant and an invertebrate (claim 7); a plant and a nematode (claim 22); a plant and a plant (claim 12), a vertebrate and a vertebrate (claim 13), an invertebrate and an invertebrate (claim 14); or a nematode and a second eukaryotic organism (claim 9) in screens to identify compounds that inhibit or reduce the pathogenicity of a single pathogen, nor do the references discuss or suggest appellants' claimed screening methods that exploit "fast killing" conditions (claims 20 and 29) as described in appellants' specification. Similarly, no reference of record teaches or suggests that the combination of an insect and a second eukaryotic organism (claim 15) may be used to identify compounds that inhibit or reduce the pathogenicity. Again, each of the references fails to recognize the existence of overlapping, common virulence factors that facilitate the particular screening methods of these claims, and no position to the contrary has been raised by the Office.



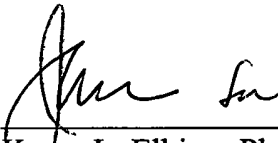
Conclusion

Appellants respectfully request that the § 103 rejection of claims 1-24, 26, and 28-30 be reversed.

This Reply Brief is being filed on November 12, 2002, which is within two months of the September 9, 2002 mailing date of the Examiner's Answer, because November 9<sup>th</sup> was a Saturday and November 11<sup>th</sup> was a federal holiday. If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 12 November 2002

  
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